STASTISTICAL SUPPLEMENENTAL TEXT:

Formal definition of indirect and direct effects

To fully understand direct and indirect effects, it is necessary to introduce the concept of the counterfactual value of the long-term outcome assuming particular values for *both* the SBP intervention and ΔeGFR%. The notation used to describe this counterfactual value is written as Y(a,m), where Y(a,m) represents the value that the long-term outcome would take if the treatment is set to the value a and the mediator (ΔeGFR%) is set to the value m. Thus, if we take a=0 to represent the standard SBP intervention and a=1 to represent the intensive intervention, Y(0,0) represents the value of the long term outcome under the standard SBP intervention if ΔeGFR% is set to 0, Y(1,0) represents the value of the long term outcome under the intensive SBP intervention if ΔeGFR% is set to 0, and Y(1,-20%) represents the value of the long term outcome under the intensive SBP intervention if ΔeGFR% is set to –20%.

There are two types of direct effects: controlled and natural. The controlled direct effect of the intensive SBP intervention when ΔeGFR% is set to a fixed value of m is based on a comparison of Y(1,m) vs. Y(0,m). If there is an interaction between the treatment and ΔeGFR%, the controlled direct effect will differ for different values of ΔeGFR%. The natural pure direct effect is defined by the comparison of Y(1,m(0)) vs Y(0,m(0)). For an individual patient, this represents the direct effect of the intensive SBP intervention when ΔeGFR% for that patient is fixed at ΔeGFR%(0), which is the value that ΔeGFR% would take without the intensive SBP treatment. Note that in contrast to the controlled direct effect in which the mediator is fixed to the same value for all patients, the natural direct effect fixes the value of ΔeGFR% to be different values for different patients, depending on the value of ΔeGFR% that would have been observed for each patient under the standard SBP intervention. Similarly, the total natural direct effect is based on the comparison of Y(1,m(1)) vs Y(0,m(1)). For an individual patient, this represents the direct effect of the intensive SBP intervention when ΔeGFR% for that patient is fixed at ΔeGFR% (1), which is the value that ΔeGFR% would take with the intensive SBP treatment. Typically, the controlled direct effect is provided for a collection of different values of the mediator, and the natural pure and total direct effects are averaged over all the patients in the study.

For an individual patient, the pure natural indirect effect is defined by the comparison of Y(0,m(1)) vs. Y(0,m(0)). This represents the effect of changing ΔeGFR% from ΔeGFR%(0) to ΔeGFR%(1) under the standard SBP intervention. This indicates the effect of changing ΔeGFR% from the value it would take under the standard SBP intervention to the value it would take under the intensive SBP intervention, but otherwise holding the SBP treatment fixed at standard SBP control. Similarly, the total natural indirect effect is defined by the comparison of Y(1,m(1)) vs. Y(1,m(0)). This represents the effect of changing ΔeGFR% from ΔeGFR%(0) to ΔeGFR%(1) under the intensive SBP intervention. This indicates the effect of changing ΔeGFR% from the value it would take under the standard BP intervention to the value it would take under the intensive SBP intervention, but otherwise holding the SBP treatment fixed at intensive SBP control.

If we assume that we are able to control confounding, and that our statistical models are correctly specified, the overall hazard ratio that defines the total effect of the SBP intervention on a long term outcome can be decomposed approximately as $HR_{TOT} = HR_{NDE} \times HR_{NIE}$, where HR_{TOT} is the hazard ratio comparing the hazard of the long-term outcome under the intensive vs. standard SBP control, HR_{NIE} is the hazard ratio for the total natural indirect effect, and HR_{NDE} = Pure natural direct effect. This is the

most common approach to the decomposition of the total effect into direct and indirect effects, and this is the approach we have taken in the text of the manuscript, where we have used the simpler phrases direct effect and indirect effect as shorthand for the pure natural direct effect and the total natural indirect effect, respectively. See VanderWeele [19]for further details on the definition of the indirect and direct effects.

Further Evaluation of Assumptions Required for Estimation of Direct and Indirect Effects.

As we described in the text of the primary manuscript, the causal interpretations of the estimated direct and indirect effects in our analyses depend on two key assumptions:

A1) The baseline covariates included in the regression models must control for all confounding between ΔeGFR% and the long-term clinical outcomes, and

A2) The effect of changes in ΔeGFR% on the long-term clinical outcomes must be the same irrespective of whether these changes are caused by the SBP intervention or other causes.

We note that in addition to these assumptions, in observational studies it is also necessary that the baseline covariates included in the analysis are sufficient also to control for confounding between the treatment and the mediator, and also between the treatment and the long-term outcomes. Fortunately, the randomized assignment of the SBP intervention assures that these latter two assumptions are satisfied in our analyses.

To address assumption A1, the primary manuscript included a comprehensive strategy for adjustment for baseline covariates, as well as sensitivity analyses which provided some reassurance that residual confounding due to a covariate that was unmeasured in the SPRINT data base is unlikely to have altered the conclusions of our analyses. The possibility also exists that a follow-up confounder, occurring after randomization, jointly influenced both ΔeGFR% and the long term clinical endpoint. The most salient possible confounder of this type is the change in SBP from baseline to 6 months, which varied within each of the two randomized SBP groups in spite of the specification of fixed target SBP levels (≤120 mm Hg and ≤140 mm Hg, respectively). The simple strategy of adding the 6-month change in SBP to the baseline covariates in the full mediation analyses estimating the indirect and direct effects of the SBP intervention would not have been valid, since the 6-month changes in SBP is a post randomization factor that is affected by the treatment. However, it is possible to investigate of effect of omitting the 6-month change in SBP from the Cox regressions of the second part of the mediation analyses that related the CVD and mortality endpoints to ΔeGFR% after controlling for the randomized SBP group and the 10 baseline covariates. Adding the change in SBP as an additional covariate in these analyses changed the HR relating ΔeGFR% to the long-term clinical endpoints by less than 1%, from 0.985 to 0.982 for the primary CVD outcome, and from 0.967 to 0.961 for all-cause mortality. These small changes suggest that confounding by early change in SBP is unlikely to have substantially affected our conclusions.

Assumption A2 is an expression of the consistency assumption of causal inference[26] in the context of our analyses. The major threat to the validity of this assumption is that measurement error is likely to have contributed substantially to the variation of ΔeGFR% between patients within the two SBP arms. This is because the change in eGFR is calculated over a relatively short time interval, so that variation in change in true GFR is not likely to have greatly exceeded variation due to measurement error. On the other

hand, it is likely that the effect of the intensive SBP intervention on ΔeGFR% resulted from treatment effects on true GFR. Thus, measurement error in ΔeGFR% may have diluted the estimated effect of ΔeGFR% on the clinical endpoints in the Cox regression models of the mediation analysis, leading to underestimation of the true indirect effects and overestimation of the true direct effects. To assess this risk, we noted that the HR comparing all-cause mortality between an eGFR of 45 ml/min/1.73m^2 and an eGFR of 95 ml/min/1.73m^2 was 1.38 in a large meta-analysis of 10 cohorts with 266,975 patients [27]. Due to the wide range of eGFR in this analysis, dilution of this estimated effect due to measurement error can be assumed to be negligible. Under the assumption of a linear relationship between the log transformed HR and the eGFR level, the HR of 1.38 translates to an HR of approximately 1.018 for the mean difference of 3.31 ml/min/1.73m^2 in eGFR between the intensive and standard SBP groups. The same meta-analysis reported a HR of 1.73 for CV death. If this HR of 1.73 is assumed to apply to the CVD composite, we would obtain a HR of approximately 1.037 for the mean difference of 3.31 ml/min/1.73m^2 in eGFR between the SBP groups. Thus, for both the mortality and the CVD outcomes, it is likely that the HR for the indirect effect of treatment through ΔeGFR% would remain clinically negligible, below 1.04, after accounting for measurement error.

Supplemental Table 1: Covariates selected by stepwise regression for CV composite and all-cause death

Candidate variables for stepwise regression	Selected for CV composite	Selected for all-cause death
	(N=22)	(N=16)
Baseline Demographic		
Alcohol abuse		X
Hispanic		
Insurance coverage is private/other		
Live with other adults		X
Marital status		
Retired	X	
Unemployed or laid off		
Working part time for pay		
Works full time	X	X
Baseline body examination and lab measurement		
Average of 3 seated heart rate	X	X
Body Mass Index		
Serum Glucose		
Serum HDL-cholesterol		

Serum LDL-cholesterol		
Serum Triglycerides		
Serum Total Cholesterol		
Serum Potassium		
Serum Sodium	X	
Baseline comorbidity conditions		
Acute coronary syndrome		
Anemia or low blood count		
Anxiety or panic disorder		X
Atrial fibrillation/atrial flutter	X	
Bipolar or manic depressive disorder	X	
Coronary artery disease		X
Coronary revascularization (CABG, PCI)		
Depression	X	
Dizziness or light headed feeling when standing		
Family heart disease		
Frailty Index	X	X
Hip problems	X	
History of cancer (not including skin cancer unless melanoma)		
Hypertension/high blood pressure		X

Irregular heart beat		
Left ventricular hypertrophy by CV, CVP or SL.	X	X
MMAS group		
Montreal Cognitive Assessment (MoCA)	X	X
Osteoarthritis or degenerative arthritis	X	
Peripheral vascular disease		
Post-traumatic stress disorder		
Stroke		
Subclinical cardiovascular disease		
Thyroid disease		
Transient ischemic attack /warning stroke	X	
Weak heart/congestive heart failure/fluid on the lungs		
Baseline medications		
Defined daily dosage of antihypertensive medications	X	X
Number of antihypertensive medications	X	
Number of non-antihypertensive medications	X	X
Therapeutic intensity score of all antihypertensive medications	X	X
Using alpha-blocker	X	
Using ACEI or ARB	X	
Using aspirin		

Using beta-blocker		X
Using calcium channel blockers	X	
Using loop diuretic		
Using Nsaid		
Using other antihypertensive medication	X	
Using statin		X
Using thiazide diuretic	X	X

Supplemental Table 2. Clinical characteristics by randomized SBP arm (N=8526)

	Standard SBP arm	Intensive SBP arm	p-value
	N=4,256	N=4,270	
	(50.0%)	(50.0%)	
Baseline Age (year)	67.8 ± 9.3	67.8 ± 9.3	0.88
Female (%)	34	36	0.21
African American (%)	31	31	0.7
Never smoked (%)	44	44	0.74
Baseline Cardiovascular disease (%)	15	16	0.59
Baseline Framingham 10-yr risk score	22 (15-32)	22 (15-32)	0.55
Baseline SBP (mm Hg)	140 ± 15	139 ± 16	0.54
Baseline DBP (mm Hg)	78 ± 12	78 ± 12	0.53
Δ SBP (6 m – baseline) (mm Hg)	-5 ± 18	-18 ± 18	<0.001
Δ DBP (6 m – baseline) (mm Hg)	-3 ± 10	-9 ± 11	<0.001
Baseline CKD (%)	28	29	0.61
Baseline MDRD eGFR (ml/min/1.73 m^2)	72 ± 20	72 ± 21	0.85
Baseline Urine ACR (mg/g)	9 (6-21)	10 (6-20)	0.36

Data are presented as mean ± SD or median (IQR) for continuous measures and % for categorical measures

Supplemental Table 3: Sensitivity Mediation Analysis with Covariates Chosen by Stepwise Regression for the Effect of the SBP Intervention on the CVD Composite and All-cause Mortality

Type of Effect	**CV Composite**		**All-cause Mortality**	
	Risk Ratio	95% CI	Risk Ratio	95% CI
Indirect	**0.99**	**0.95 to 1.04**	**1.00**	**0.96 to 1.04**
Direct	**0.65**	**0.54 to 0.78**	**0.75**	**0.58 to 0.92**
Total	**0.65**	**0.54 to 0.77**	**0.75**	**0.59 to 0.91**

The total effects of the SBP intervention on the CVD composite and all-cause mortality can be represented approximately as the product of the indirect and direct effects. Thus, for the CVD composite, 0.65 = 0.99 x 0.65. For all cause-mortality, 0.75=1.00 x 0.75.

Model adjusted for baseline age, gender, race, systolic blood pressure, diastolic blood pressure, cardiovascular disease, smoking, eGFR, urine albumin / creatinine ratio, Framingham 10-year cardiovascular disease risk score and additional covariates chosen by stepwise regression.

Supplemental Table 4: Sensitivity Mediation Analysis of CVD Composite Including Patients with CVD Composite Events Prior to 6 Months. (N=8611)

Type of Effect	**Model 1***		**Model 2****	
	Risk Ratio	95% CI	Risk Ratio	95% CI
Indirect	**0.98**	**0.95 to 1.02**	**0.99**	**0.95 to 1.03**
Direct	**0.73**	**0.61 to 0.85**	**0.70**	**0.57 to 0.81**
Total	**0.71**	**0.60 to 0.84**	**0.69**	**0.57 to 0.80**

The total effects of the SBP intervention on all-cause mortality can be represented approximately as the product of the indirect and direct effects. Thus, for model 1, 0.71 = 0.98 x 0.73; For model 2, 0.69=0.99 x 0.70.

*Model 1 adjusted for baseline age, gender, race, systolic blood pressure, diastolic blood pressure, cardiovascular disease, smoking, eGFR, urine albumin / creatinine ratio and Framingham 10-year cardiovascular disease risk score

**Model 2= Model 1+ additional covariates chosen by stepwise regression.

Supplemental Table 5: Sensitivity Mediation Analysis of All-cause Mortality Including Patients with CVD Composite Events Prior to 6 Months. (N=8611)

Type of Effect	**Model 1***		**Model 2****	
	Risk Ratio	95% CI	Risk Ratio	95% CI
Indirect	**1.00**	**0.96 to 1.05**	**1.00**	**0.96 to 1.05**
Direct	**0.81**	**0.64 to 0.99**	**0.76**	**0.60 to 0.92**
Total	**0.81**	**0.66 to 0.98**	**0.76**	**0.62 to 0.93**

The total effects of the SBP intervention on all-cause mortality can be represented approximately as the product of the indirect and direct effects. Thus, for model 1, 0.81 = 1.00 x 0.81; For model 2, 0.76=1.00 x 0.76.

*Model 1 adjusted for baseline age, gender, race, systolic blood pressure, diastolic blood pressure, cardiovascular disease, smoking, eGFR, urine albumin / creatinine ratio and Framingham 10-year cardiovascular disease risk score

**Model 2= Model 1+ additional covariates chosen by stepwise regression.

Supplemental Table 6. Adjusted Risk Difference (%) between the Standard and Intensive SBP Arms Controlling for ΔeGFR%.

Risk factors*	Adjusted risk difference (%, Intensive vs. Standard) and 95% CI
Baseline Demographic	
Alcohol abuse	-0.11 (-0.94, 0.84)
Hispanic	0.23 (-1.09, 1.32)
Insurance coverage is private/other	1.63 (-0.49, 2.14)
Live with other adults	0.42 (-1.52, 1.94)
Marital status (Divorced vs. Others)	0.25 (-0.78, 1.03)
Marital status (Living in a marriage-like relationship vs. Others)	-0.10 (-0.49, 0.39)
Marital status (Married vs. Others)	-0.99 (-2.59, 1.59)
Marital status (Never marrried vs. Others)	0.02 (-0.70, 0.71)
Marital status (Separated vs. Others)	-0.20 (-0.59, 0.38)
Marital status (Widowed vs. Others)	0.13 (-0.79, 1.05)
Retired	0.62 (-1.49, 2.11)
Unemployed or laid off	-0.42 (-1.44, 1.02)
Working part time for pay	-1.70 (-3.15, 1.43)

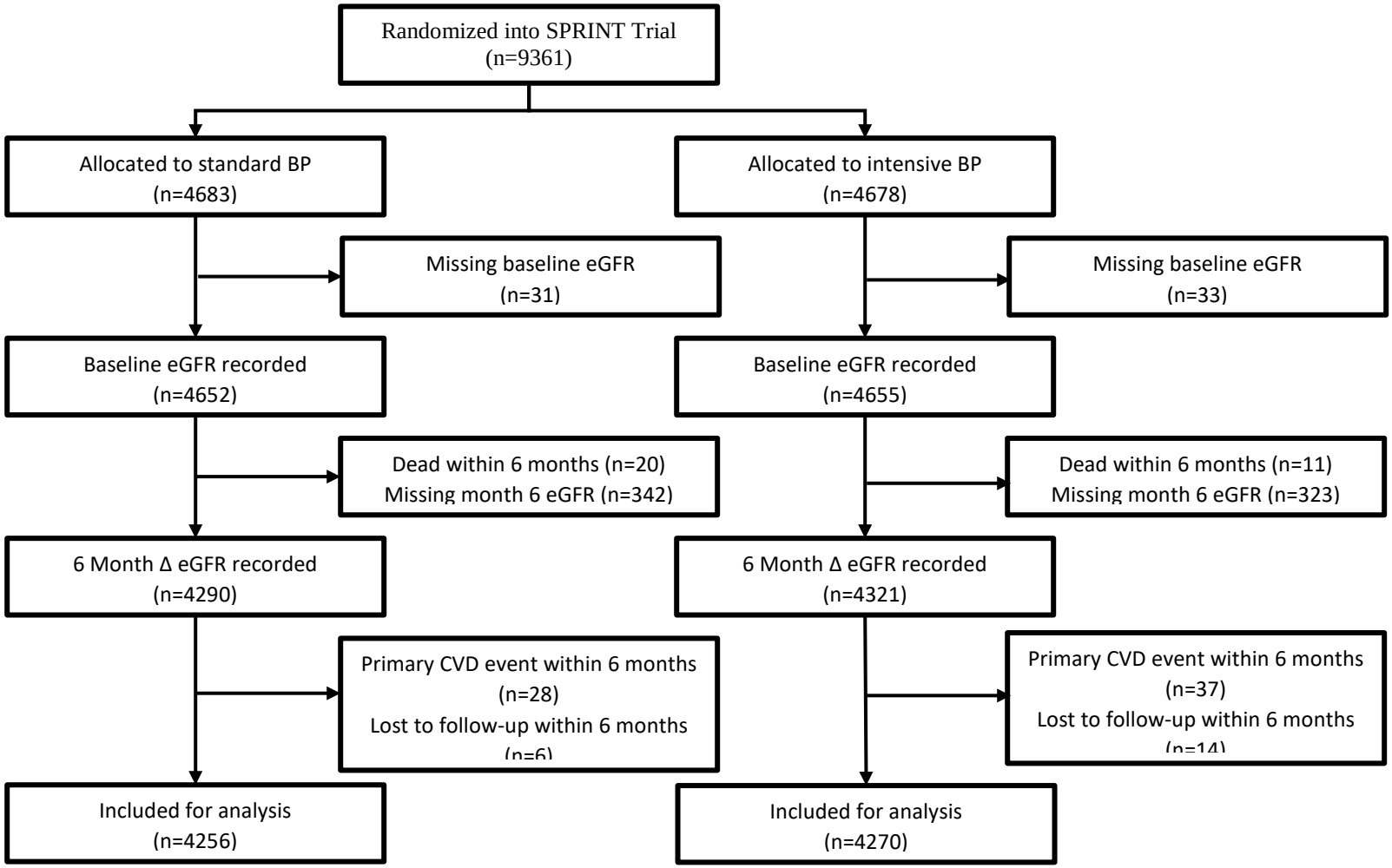
Works full time	-0.04 (-1.82, 1.78)
Baseline body examination and lab measurement	
Average of 3 seated heart rate (Median=65)	-0.23 (-2.37, 2.14)
Body Mass Index (Median=29.0)	-0.51 (-2.67, 2.15)
Serum Glucose (Median=97)	-0.38 (-2.53, 2.14)
Serum HDL-cholesterol (Median=50)	0.75 (-1.39, 2.16)
Serum LDL-cholesterol (Median=110)	1.33 (-0.83, 2.17)
Serum Triglycerides (Median=107)	0.39 (-1.76, 2.15)
Serum Total Cholesterol (Median=187)	0.70 (-1.44, 2.15)
Serum Potassium (Median=4.2)	1.07 (-1.06, 2.14)
Serum Sodium (Median=140)	-0.14 (-2.28, 2.14)
Baseline comorbidity conditions	
Acute coronary syndrome	0.51 (-0.39, 0.91)
Anemia or low blood count	0.00 (-1.39, 1.39)
Anxiety or panic disorder	0.96 (-0.30, 1.27)
Atrial fibrillation/atrial flutter	0.44 (-0.72, 1.16)
Bipolar or manic depressive disorder	0.19 (-0.38, 0.58)
Coronary artery disease	0.68 (-0.76, 1.45)
Coronary revascularization (CABG, PCI)	0.22 (-1.03, 1.25)
Depression	0.36 (-1.29, 1.65)

Dizziness or light headed feeling when standing	0.09 (-0.78, 0.86)
Family heart disease	2.51 (0.39, 2.14)
Frailty Index (Median=0.16)	1.18 (-0.97, 2.16)
Hip problems	-0.51 (-2.01, 1.49)
History of cancer (not including skin cancer unless melanoma)	0.78 (-0.62, 1.41)
Hypertension/high blood pressure	1.32 (0.21, 1.12)
Irregular heart beat	0.71 (-0.89, 1.61)
Left ventricular hypertrophy by CV, CVP or SL.	-1.07 (-2.81, 1.73)
MMAS group (High=8 vs. Others)	1.63 (-0.43, 2.07)
MMAS group (Low<6 vs. Others)	-0.18 (-1.86, 1.67)
MMAS group(Medium 6-8 vs. Others)	-0.43 (-2.50, 2.06)
Montreal Cognitive Assessment (MoCA) (Median=23.0)	1.78 (-0.37, 2.17)
Osteoarthritis or degenerative arthritis	-0.13 (-2.04, 1.91)
Peripheral vascular disease	-0.15 (-1.12, 0.96)
Post-traumatic stress disorder	0.53 (-0.38, 0.92)
Stroke	0.10 (-0.21, 0.31)
Subclinical cardiovascular disease	-0.32 (-1.21, 0.89)
Thyroid disease	0.93 (-0.41, 1.35)
Transient ischemic attack /warning stroke	-0.54 (-1.25, 0.70)
Weak heart/congestive heart failure/fluid on the lungs	0.30 (-0.48, 0.78)

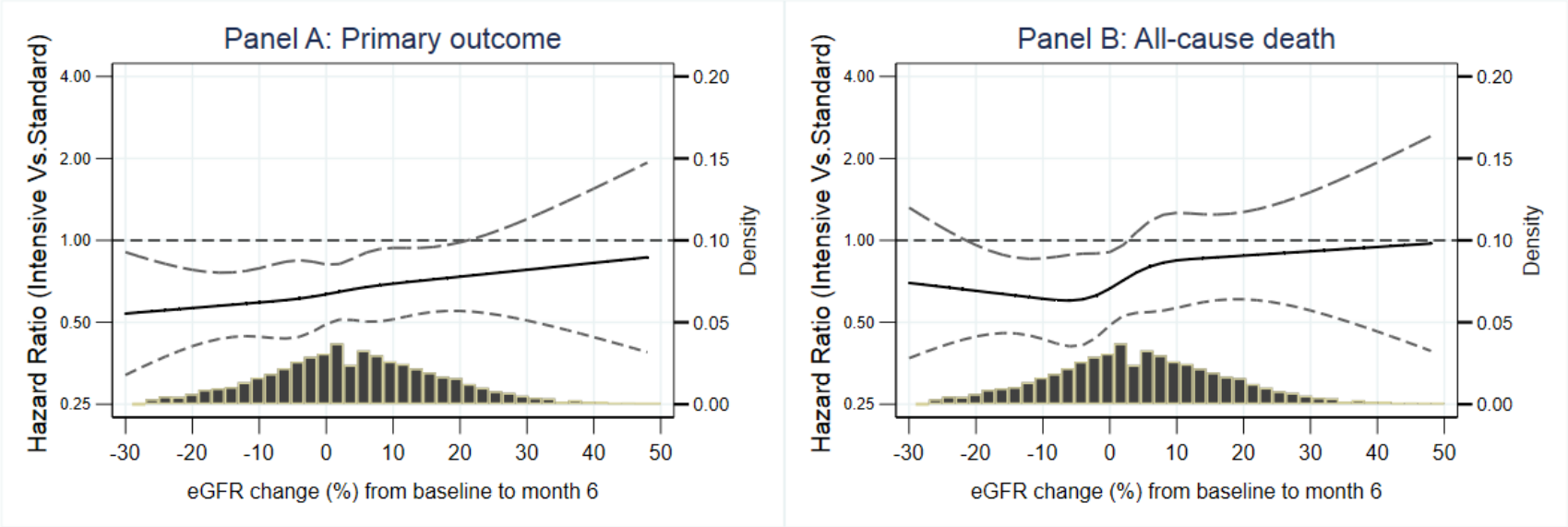
Baseline medications	
Defined daily dosage of antihypertensive medications (Median=2.0)	0.13 (-2.02, 2.15)
Number of antihypertensive medications (Median=2.0)	0.42 (-1.55, 1.98)
Number of non-antihypertensive medications (Median=3.0)	0.02 (-2.11, 2.13)
Therapeutic intensity score of all antihypertensive medications (Median=0.74)	-1.39 (-3.54, 2.13)
Using alpha-blocker	-0.19 (-1.49, 1.31)
Using ACEI or ARB	1.38 (-0.73, 2.13)
Using aspirin	1.68 (-0.46, 2.16)
Using beta-blocker	3.01 (0.94, 2.10)
Using calcium channel blockers	-1.49 (-3.54, 2.04)
Using loop diuretic	0.42 (-0.58, 1.00)
Using Nsaid	2.61 (0.53, 2.11)
Using other antihypertensive medication	0.58 (-0.25, 0.84)
Using statin	-1.74 (-3.87, 2.11)
Using thiazide diuretic	-1.61 (-3.72, 2.09)

* Continuous covariates were dichotomized by their median values (> median vs. ≤ median)

Supplemental Figure 1: CONSORT Flowchart



Supplemental Figure 2: Controlled Direct Effects of SBP Intervention at Different Levels of ΔeGFR% with Covariates Chosen by Stepwise Regression



Model adjusted for baseline age, gender, race, systolic blood pressure, diastolic blood pressure, cardiovascular disease, smoking, eGFR, urine albumin / creatinine ratio, Framingham 10-year cardiovascular disease risk score and additional covariates chosen by stepsie regression

The figure displays the estimated controlled direct effects of the intensive SBP intervention on the CVD composite (Left) and all-cause mortality (right) when early change in eGFR is held fixed at the values indicated on the horizontal axis. The interaction p-values between early change in eGFR and the randomized SBP group are 0.37 for the CVD composite and 0.35 for all-cause mortality, indicating that controlled direct effects do not differ significantly between different levels of early change in eGFR.